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(54) Title: NEW PROCESS FOR THE PREPARATION OF AMENAMEVIR

(57) Abstract: The present invention relates to an improved process for the preparation of Amenamevir and derivatives thereof via a four component Ugi reaction.

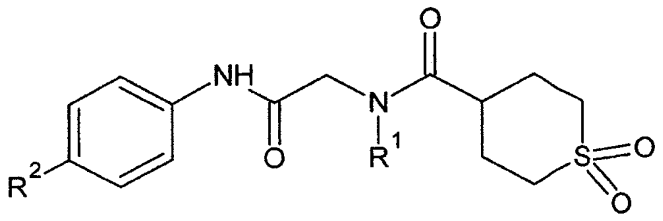
New process for the preparation of Amenamevir

The present invention relates to an improved process for the preparation of Amenamevir and derivatives thereof via a four component Ugi reaction.

Amenamevir is a helicase-primase inhibitor that is active against varicella-zoster virus and herpes simplex virus types 1 and 2. Amenamevir stabilizes the interaction between the helicase-primase and its DNA substrates, preventing the progression through helicase or primase catalytic cycles, thus interfering with viral DNA replication and viral growth. Amenamevir is marketed under the name Amenalief® by the company Maruho Co., Ltd for the treatment of herpes zoster (shingles) in Japan.

A synthesis of Amenamevir and derivatives thereof is e.g. disclosed in EP 1 844 775 B1. Since the technical synthesis of Amenamevir is rather long and inefficient, it has been the object of the present invention to provide an improved process for the preparation of Amenamevir and derivatives thereof.

The present invention provides a process for the preparation of a compound of formula (I):



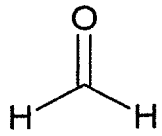
(I)

wherein

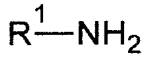
R^1 is a phenyl group which phenyl group is substituted by at least one methyl group and which phenyl group may further have one or two substituents selected from the group consisting of a methyl group and halogen atoms; or a 5-indanyl group; and

R^2 is a 1,2,4-oxadiazol-3-yl or 4-oxazolyl group;

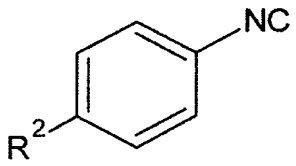
which process is characterized in that compounds of formulas (II), (III), (IV) and (V) are reacted with each other:



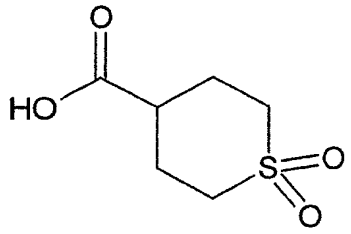
(II)



(III)



(IV)



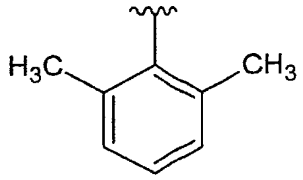
(V).

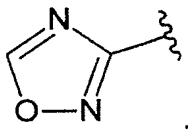
The process of the present invention is preferably based on a four component Ugi reaction.

The formaldehyde of formula (II) is preferably used in the form of paraformaldehyde.

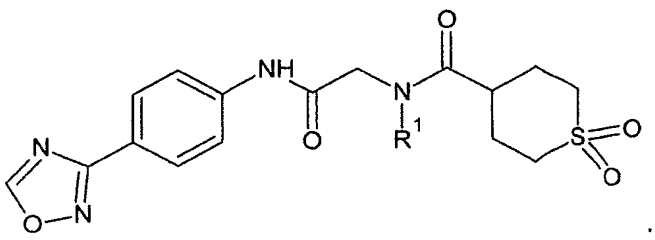
The term "halogen atoms" refers to F, Cl, Br and I.

Preferably, R^1 is a phenyl group which is substituted by two methyl groups.

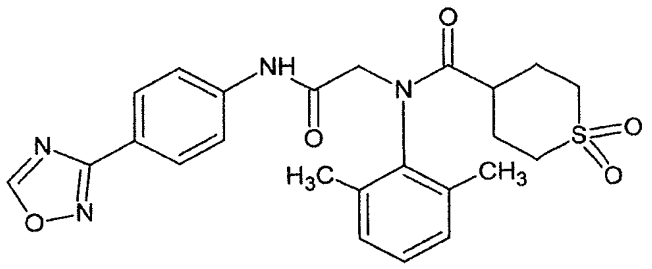
Especially preferably, R^1 is a group of formula  .

Preferably, R^2 is a 1,2,4-oxadiazol-3-yl group:  .

A preferred compound of formula (I) is the following compound:



The most preferred compound of formula (I) is the following compound (Amenamevir):



Preferably, the compounds of formulas (II), (III), (IV) and (V) are reacted with each other in a one-pot reaction; preferably in a simultaneous one-pot reaction.

The process of the present invention can be carried out in any solvent suitable for a four component Ugi reaction. Examples of suitable solvents include 2,2,2-trifluoroethanol (TFE), methanol, ethanol, butanol, n-propanol, isopropanol, glycol, glycerine, water, mixtures of one or more of the above alcohols and water, biphasic solvent mixtures such as water mixed with DMF, HMPT, DCM, chloroform, toluene, benzene or chlorobenzene as well as mixtures of one or more of these solvents.

Preferred solvents include polar solvents such as methanol, ethanol, 2,2,2-trifluoroethanol, n-propanol, isopropanol, water or mixtures thereof. Methanol is an especially preferred solvent.

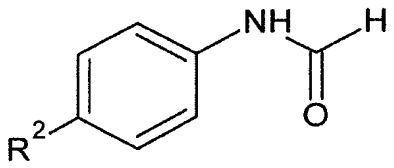
The process of the present invention can be performed in a temperature range from -40 °C to up to 100 °C. Preferably, the process is performed between room temperature and 50 °C. Most preferably the process is performed at room temperature (such as about 20-25 °C) since this does not require any cooling or heating efforts.

Typically, the process is performed over a time period of at least 24 hours, preferably 1-4 days, preferably at room temperature.

The relative amounts of the 4 starting compounds of formulas (II), (III), (IV) and (V) are not particularly limited. Good results can be obtained when using about equimolar amounts. For example, each of the compounds of formulas (II), (IV) and (V) may initially be present in an amount of 0.9-1.3 equivalents relative to the amount of the amine of formula (III). Preferably, the components are added in equal or small excess amounts (1.0-1.2 eq) in relation to the amine of formula (III).

The process of the present invention can also be performed with the formamide precursor of the isocyanide with an in situ formation of the isocyanide and subsequent addition of the other components, thus allowing for a "one-pot" process.

According to a preferred embodiment, the isocyanide (IV) is prepared in situ from the corresponding formamide of formula (VI):



(VI).

This procedure avoids the isolation of the noxious isocyanide, is shorter and saves synthetic steps. In this embodiment the formamide is first converted in situ to the isocyanide using a suitable dehydrating agent and a base. Then, the other starting materials of the Ugi reaction (acid, aldehyde and amine), preferably in a suitable co-solvent, are added.

Accordingly, in one embodiment the process of the invention comprises reacting a formamide precursor (VI) of a compound of formula (IV) in the presence of a dehydrating agent and a base to produce *in situ* the compound of formula (IV), followed

by adding the compounds of formula (II), (III) and (V) (preferably in a suitable co-solvent) to initiate the Ugi reaction.

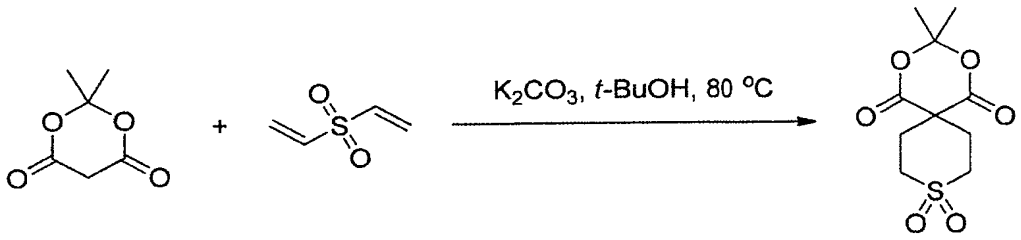
Exemplary dehydrating agents are phosphorous oxychloride, thionyl chloride, tosylchloride, phosgene, diphosgene, triphosgene. Suitable bases include TEA, pyridine, Hunig's, KOtBu base, NaOH or KOH. Suitable solvents for the dehydration reaction are DCM, chloroform, toluene, xylene, benzene or 1,3-dimethyl benzene. Examples of suitable co-solvents for the Ugi reaction include methanol, ethanol, propanol, butanol, glycol, glycerine, trifluoroethanol or aqueous mixtures thereof.

The dehydration part of the reaction can be performed under cooling with an ice bath or any other suitable cooling mixture.

EXAMPLES

1. Synthesis of compound (V):

1.1 Synthesis of 3,3-Dimethyl-2,4-dioxa-9-thiaspiro[5.5]undecane-1,5-dione-9,9-dioxide:

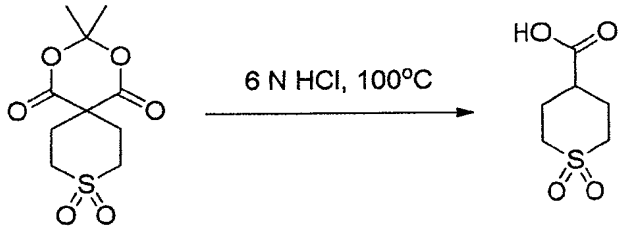


Divinylsulfone (5.89 g, 49.8 mmol) was charged to refluxing tert-butanol (80 °C, 100 mL, 1070 mmol) followed by addition of K_2CO_3 (1.72 g, 12.5 mmol, reagent grade powder, -325 mesh). 2,2-Dimethyl-1,3-dioxane-4,6-dione (8.60 g, 59.8 mmol) was added in five portions over 30 min to the reaction solution at 80 °C. The reaction was stirred at 80 °C for 1 h or until HPLC showed complete consumption of the divinylsulfone. The reaction was cooled to 35 °C, and MtBE (20.0 mL, 168 mmol) was added. The slurry was stirred at 35 °C for 12 h and then filtered; the cake was dried in a vacuum oven at 60 °C, with N_2 bleed, overnight. The desired adduct was isolated as

a white solid in near quantitative yield (13.0 g, 496 mol, >98% yield). The ^{1}H NMR of the product was consistent with that reported in the literature for this compound.

Ref: E. Carlon , R. W. Draper, R. Friary **(1977)** A Brief Preparation of Thian-4-Carboxylic Acid 1,1-Dioxide, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 1977, 9, 94-96.

1.2 Thian-4-carboxylic Acid 1,1-Dioxide:



3,3-Dimethyl- 2,4-dioxa-9-thiaspiro[5.5]undecane-1,5-dione-9,9-dioxide 1 (20.0 g, 76.3 mmol) and then 6 N hydrochloric acid (60 mL) and Antifoam 204 (200 mg, 1 wt % relative to 1) were charged to a 250-mL, three-neck round-bottom flask, equipped with a mechanical stirrer and a thermocouple. The reaction was then heated to reflux and the distillate collected until the internal temperature reached 100 °C; thereafter the reaction was allowed to reflux for an additional 8 h or until LC/MS showed complete conversion of 1 to 2. The reaction was then cooled to room temperature and held for ~12 h, during which time the product crystallized from solution. The slurry was cooled to 0 °C for 1 h and then filtered. The cake was dried in a vacuum oven at 60 °C, with nitrogen bleed, overnight to give the product as a white, crystalline solid (8.84 g, 49.6 mmol, 65% yield, >98 wt % by quantitative ^{1}H NMR vs benzyl benzoate standard). ^{1}H NMR of compound (V) was consistent with that reported in the literature.

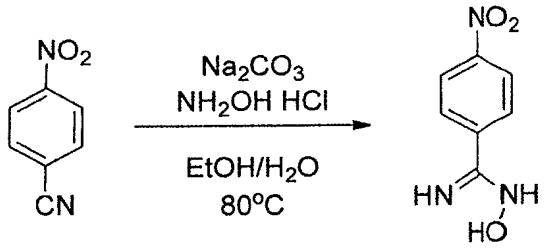
Ref: Matthew. M. Bio, Karl B. Hansen, John Gipson **(2008)** A Practical, Efficient Synthesis of 1,1-Dioxo-hexahydro-1λ^6-thiopyran-4-carbaldehyde. Organic Process Research & Development 12, 892-895

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dt, J = 8.3, 5.4 Hz, 4H), 7.05 (td, J = 8.5, 3.3 Hz, 4H), 5.63 (s, 1H), 5.52 (s, 1H), 4.29-4.16 (m, 2H), 3.73 (dt, J = 19.5, 10.8 Hz, 2H), 3.58-3.41 (m, 2H), 3.38-3.17 (m, 2H), 2.88 (dq, J = 13.0, 6.5 Hz, 2H), 2.64-2.49 (m, 2H),

2.47-2.34 (m, 2H), 1.38 (d, J = 4.7 Hz, 7H), 1.34 (s, 5H), 1.20 (d, J = 7.0 Hz, 5H), 1.17-1.12 (m, 12H).

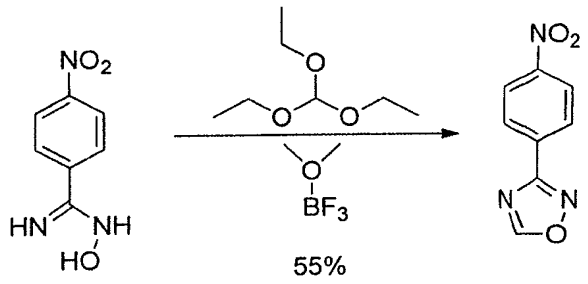
2. Synthesis of the isocyanide (IV):

2.1 Synthesis of N-Hydroxy-4-nitro-benzamidine:



Hydroxylamine hydrochloride 1.9 g, 27.2 mmol) and then sodium carbonate (2.2 g, 20.4 mmol) were added to a stirred solution of 4-nitro-benzonitrile (1 g, 6.8 mmol) in ethanol (20 mL) and water (8 mL). The resulting mixture was refluxed at 85°C under an atmosphere of nitrogen for 2 hours. The volatiles were then evaporated and the residue was extracted with ethyl acetate. The organic phases were washed with brine solution, dried over Na_2SO_4 and evaporated to afford 1.2 g (98%) of *N*-Hydroxy-4-nitro-benzamidine. ^1H NMR: (DMSO-d_6): δ 10.2 (s,1H), 8.24 (d,2H), 7.97 (d,2H), 6.03 (s, 2H).

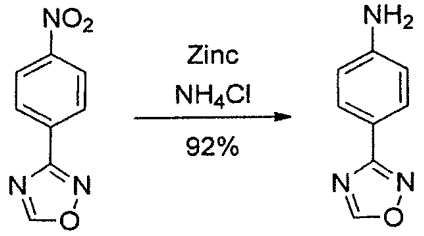
2.2 Synthesis of 3-(4-Nitro-phenyl)-[1,2,4]oxadiazole:



Triethyl orthoformate (2.93 g, 19.8 mmol) was added to a stirred solution of N-hydroxy-4-nitro-benzamidine (1.2g, 6.6 mmol) in THF (15 mL). The mixture was cooled to 0°C. Boron trifluoride dimethyl ether (900 mg, 7.9 mmol) was then added drop wise. The mixture was maintained at room temperature for three hours. The volatiles were

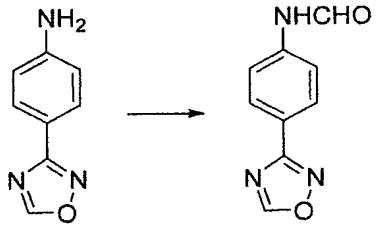
evaporated and the residue was washed with ether and dried to afford 650 mg (55%) of 3-(4-nitro-phenyl)-[1,2,4]oxadiazole.

2.3 Synthesis of 4-[1,2,4]Oxadiazol-3-yl-phenylamine:



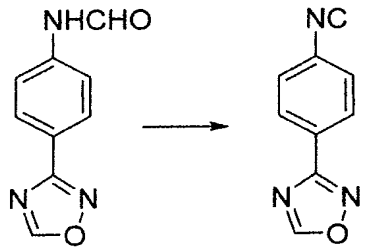
Ammonium chloride (214 mg, 4 mmol) in water (5 mL) was added to a stirred solution of 3-(4-nitro-phenyl)-[1,2,4]oxadiazole (200 mg, 1 mmol) in THF (15 mL). Zinc powder (262 mg, 4 mmol) was then added portion wise. The reaction was stirred at room temperature for 1 hour and then refluxed at 65°C for 5 hours. The mixture was filtered over celite, the filtrate was evaporated and the residue was extracted with ethyl acetate. The ethyl acetate was washed with brine solution, dried over Na_2SO_4 and evaporated to afford 155 mg (92%) of 4-[1,2,4]oxadiazol-3-yl-phenylamine.
^{1}H NMR: (DMSO-d_6): δ 9.5 (s,1H), 7.7 (d,2H), 6.7 (d,2H), 5.8 (s, 2H).

2.4 Synthesis of *N*-(4-(1,2,4-oxadiazol-3-yl)phenyl)formamide:



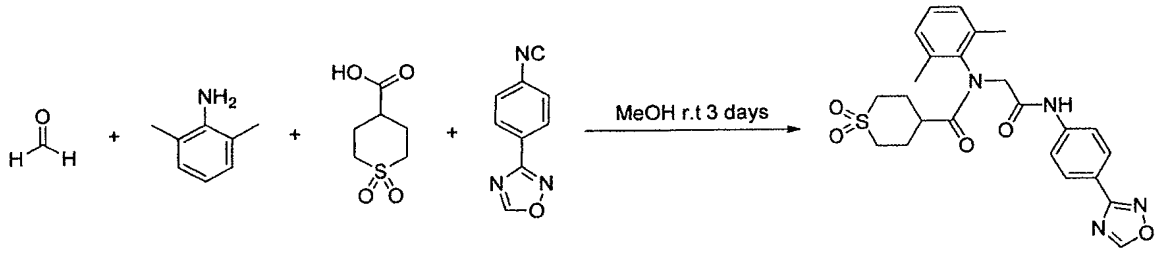
A solution of 4-(1,2,4-oxadiazol-3-yl)aniline (322 mg, 2 mmol) in ethyl formate (50 mL) was refluxed for 18 hours. The reaction was concentrated in vacuo and further dried under high vacuum.

2.5 Synthesis of 3-(4-isocyanophenyl)-1,2,4-oxadiazole:



To a solution of *N*-(4-(1,2,4-oxadiazol-3-yl)phenyl)formamide (374 mg, 2 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (10 mmol, 5.0 equiv.). The mixture was cooled to -5 °C at which $POCl_3$ (1.8 mmol, 0.9 equiv.) was added drop wise over 60 minutes maintaining the temperature below 0 °C. After the addition the reaction was stirred at 0°C for an additional hour. An aqueous solution of Na_2CO_3 (0.6 M, 30 mL) was added carefully while the temperature increased to 20°C. Additional water was added until all salts were dissolved (~50 mL). The mixture was transferred to a separatory funnel and the organic layer was separated. The water layer was extracted with dichloromethane (100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by filtration over silica (100% CH_2Cl_2) and after evaporation of the solvent obtained as a brown solid (69 %).

3. Synthesis of N-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-N-(2,6-dimethylphenyl) tetrahydro-2H-thiopyran-4-carboxamide 1,1-dioxide:

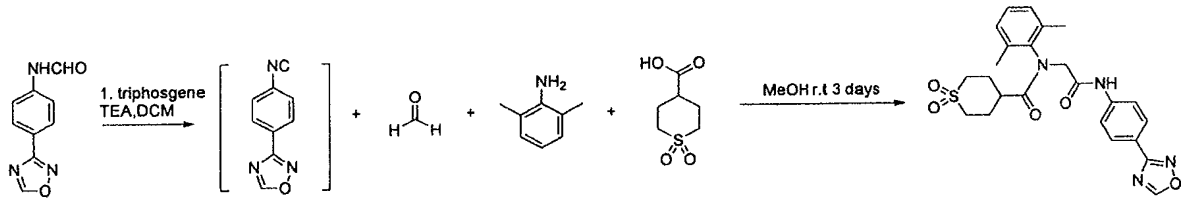


Paraformaldehyde (1.2 eq), 2,6-dimethylaniline (1.0 eq), tetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide (1.2 eq) and 3-(4-isocyanophenyl)-1,2,4-oxadiazole (1.2 eq) were added together along with MeOH and stirred at room temperature for 72h.

The solvent was evaporated under reduced pressure and the residue was purified using flash chromatography to obtain the desired bisamide product.
Other solvents which were successfully used for this reaction include ethanol, 2,2,2-trifluoroethanol, propanol, isopropanol, water and mixtures thereof.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (d, *J* = 9.8 Hz, 1H), 8.69 (dd, *J* = 9.3, 3.7 Hz, 1H), 7.64 (d, *J* = 2.8 Hz, 1H), 7.46 (td, *J* = 9.0, 5.5 Hz, 2H), 7.23 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.14 (td, *J* = 9.0, 4.6 Hz, 2H), 5.59 (d, *J* = 4.9 Hz, 1H), 4.27-4.16 (m, 1H), 3.86 (s, 3H), 3.78 (m, 1H), 3.69-3.61 (m, 1H), 3.61-3.49 (m, 1H), 3.45-3.31 (m, 1H), 3.01-2.90 (m, 1H), 2.46-2.36 (m, 2H), 2.34-2.21 (m, 2H), 1.46 (s, 12H), 1.41 (s, 4H), 1.38-1.32 (m, 4H), 1.24-1.17 (m, 9H).

4. *In situ* one-pot procedure:

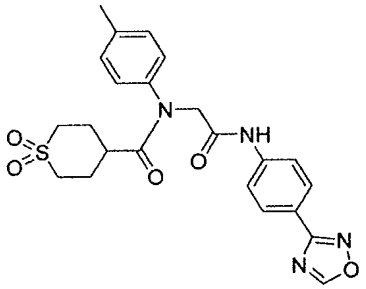


To a stirred solution of *N*-(4-(1,2,4-oxadiazol-3-yl)phenyl)formamide (1.0 mmol) in dichloromethane (1 mL), trimethylamine (2.4 mmol) was added at 0°C. After 10 min, triphosgene (0.4 mmol) was added dropwise over 30 min. The reaction mixture was stirred at 0°C for an additional 20 min and then paraformaldehyde (1.2 eq), 2,6-dimethylaniline (1.0 eq), tetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide (1.2 eq) and methanol (2 mL) were added. The solution was stirred for 48 h. The solvent was evaporated under reduced pressure and the residue was purified using flash chromatography to obtain the desired bisamide product. The analytical data was equivalent to Example 3.

5. Synthesis of further compounds of formula (I):

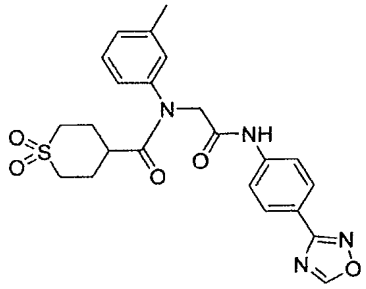
The following compounds of formula (I) were prepared according to the procedures described above using appropriate starting materials:

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(*p*-tolyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



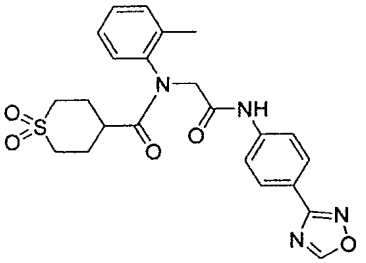
HRMS (ESI) Calcd for $C_{23}H_{25}N_4O_5S$: $[M+H]^+$: 469.1546; found 469.1580.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-N-(*m*-tolyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



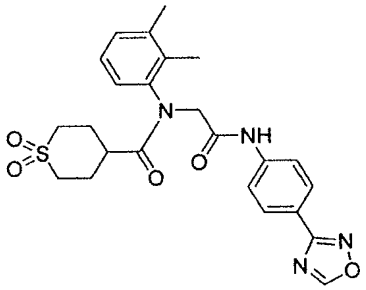
HRMS (ESI) Calcd for $C_{23}H_{25}N_4O_5S$: $[M+H]^+$: 469.1546; found 469.1544.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(*o*-tolyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



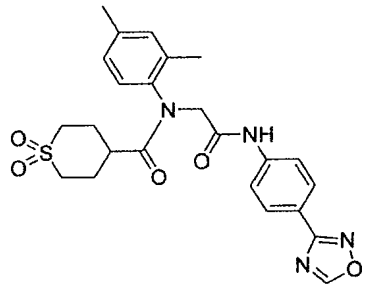
HRMS (ESI) Calcd for $C_{23}H_{25}N_4O_5S$: $[M+H]^+$: 469.1546; found 499.1598.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(2,3-dimethylphenyl) tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



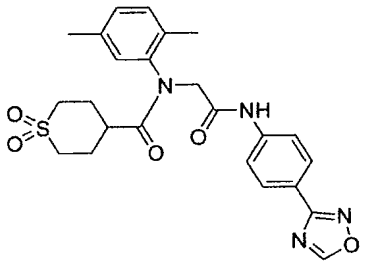
HRMS (ESI) Calcd for $C_{24}H_{27}N_4O_5S$: $[M+H]^+$: 483.1702; found 483.1711.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(2,4-dimethylphenyl) tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



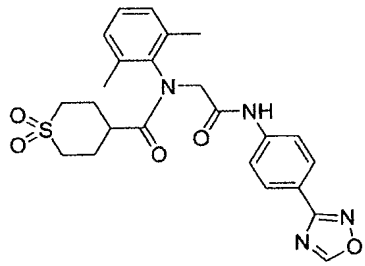
HRMS (ESI) Calcd for $C_{24}H_{27}N_4O_5S$: $[M+H]^+$: 483.1702; found 483.1700.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(2,5-dimethylphenyl) tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



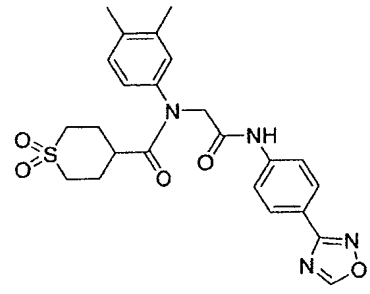
HRMS (ESI) Calcd for $C_{24}H_{27}N_4O_5S$: $[M+H]^+$: 483.1702; found 483.1703.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(2,6-dimethylphenyl) tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



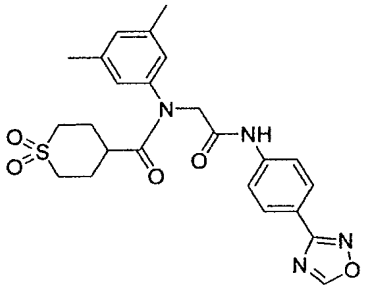
HRMS (ESI) Calcd for $C_{24}H_{27}N_4O_5S$: $[M+H]^+$: 483.1702; found 483.1800.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(3,4-dimethylphenyl) tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



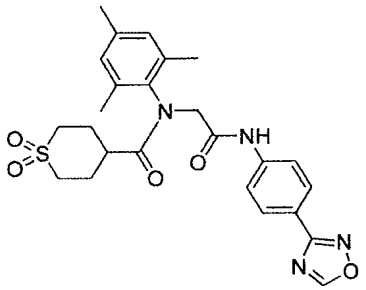
HRMS (ESI) Calcd for $C_{24}H_{26}N_4O_5S$: $[M+H]^+$: 483.1702; found 483.1714.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(3,5-dimethylphenyl) tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



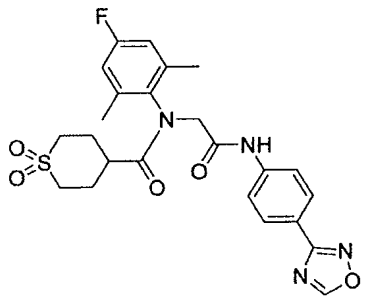
HRMS (ESI) Calcd for $C_{24}H_{26}N_4O_5S$: $[M+H]^+$: 483.1702; found 483.1704.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-mesityltetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



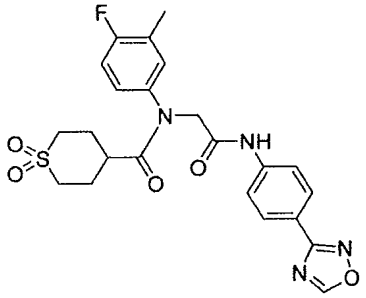
HRMS (ESI) Calcd for $C_{25}H_{29}N_4O_5S$: $[M+H]^+$: 497.1859; found 497.1955.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(4-fluoro-2,6-dimethylphenyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



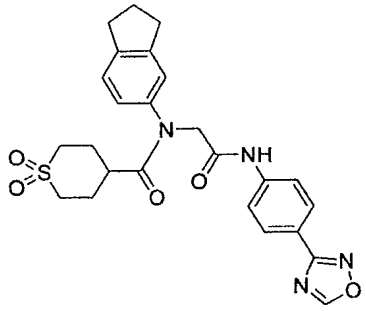
HRMS (ESI) Calcd for $C_{24}H_{26}FN_4O_5S$: $[M+H]^+$: 501.1608; found 501.1601.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(4-fluoro-3-methylphenyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



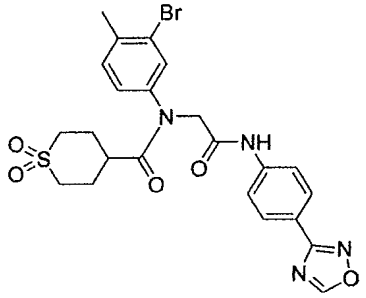
HRMS (ESI) Calcd for $C_{23}H_{24}FN_4O_5S$: $[M+H]^+$: 487.1451; found 487.1455.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(2,3-dihydro-1*H*-inden-5-yl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



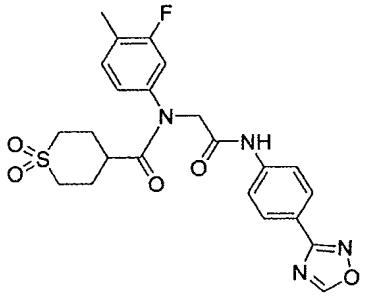
HRMS (ESI) Calcd for $C_{25}H_{27}N_4O_5S$: $[M+H]^+$: 495.1702; found 495.1700.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(3-bromo-4-methylphenyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



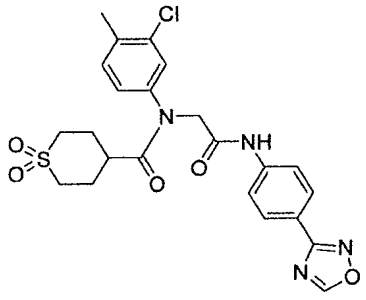
HRMS (ESI) Calcd for $C_{23}H_{24}BrN_4O_5S$: $[M+H]^+$: 547.0651; found 547.0666.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(3-fluoro-4-methylphenyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



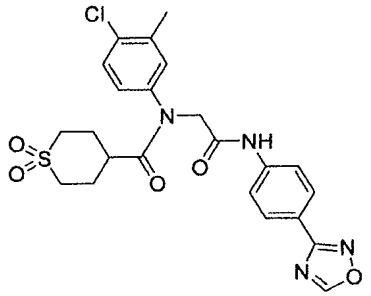
HRMS (ESI) Calcd for $C_{23}H_{24}FN_4O_5S$: $[M+H]^+$: 487.1451; found 487.1455.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(3-chloro-4-methylphenyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



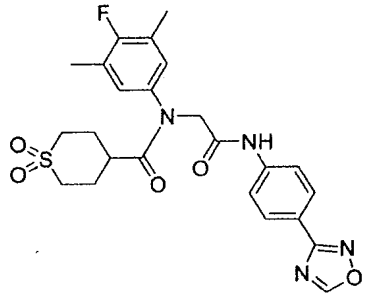
HRMS (ESI) Calcd for $C_{23}H_{24}ClN_4O_5S$: $[M+H]^+$: 503.1156; found 503.1154.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(4-chloro-3-methylphenyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



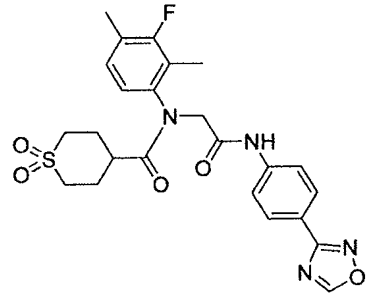
HRMS (ESI) Calcd for $C_{23}H_{24}ClN_4O_5S$: $[M+H]^+$: 503.1156; found 503.1157.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(4-fluoro-3,5-dimethylphenyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



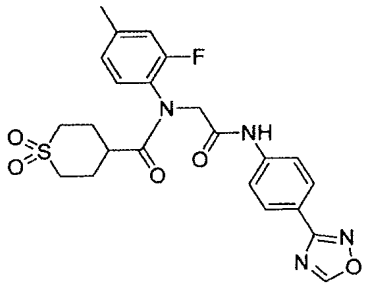
HRMS (ESI) Calcd for $C_{24}H_{26}FN_4O_5S$: $[M+H]^+$: 501.1608; found 501.1625.

***N*-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-*N*-(3-fluoro-2,4-dimethylphenyl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide**



HRMS (ESI) Calcd for $C_{24}H_{26}FN_4O_5S$: $[M+H]^+$: 501.1608; found 501.1611.

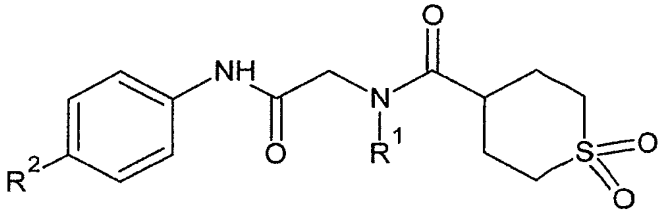
_N_-(2-((4-(1,2,4-oxadiazol-3-yl)phenyl)amino)-2-oxoethyl)-_N_-(2-fluoro-4-methylphenyl)tetrahydro-2_H_-thiopyran-4-carboxamide 1,1-dioxide



HRMS (ESI) Calcd for $C_{23}H_{23}FN_4O_5S$: $[M+H]^+$: 487.1451; found 487.1455.

Claims

1. A process for the preparation of a compound of formula (I):



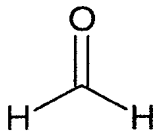
(I)

wherein

R^1 is a phenyl group which phenyl group is substituted by at least one methyl group and which phenyl group may further have one or two substituents selected from the group consisting of a methyl group and halogen atoms; or a 5-indanyl group; and

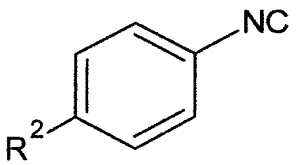
R^2 is a 1,2,4-oxadiazol-3-yl or 4-oxazolyl group;

which process is characterized in that compounds of formulas (II), (III), (IV) and (V) are reacted with each other:

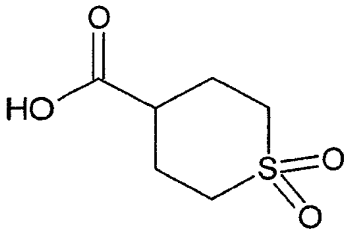


(II)

(III)



(IV)

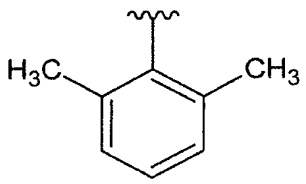


(V)

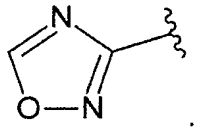
wherein the formaldehyde of formula (II) may be used in the form of paraformaldehyde.

2. The process of claim 1, wherein R^1 is a phenyl group which is substituted by two methyl groups.

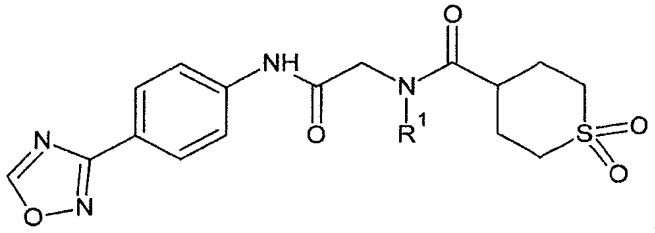
3. The process of claim 1 or 2, wherein R^1 is a group of formula



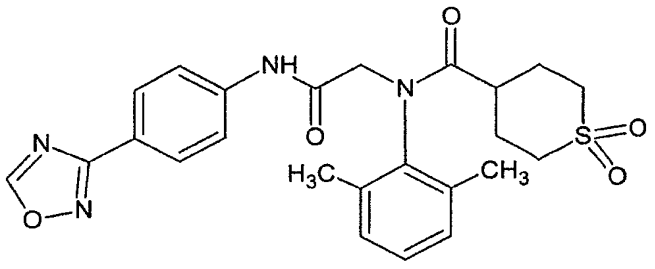
4. The process of any one of the preceding claims, wherein R^2 is a 1,2,4-oxadiazol-3-yl group:



5. The process of any one of the preceding claims, wherein the compound of formula (I) is the following compound:



6. The process of any one of the preceding claims, wherein the compound of formula (I) is the following compound (Amenamevir):

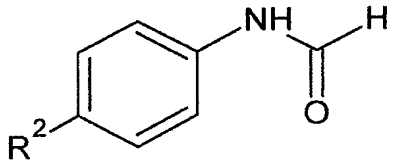


7. The process of any one of the preceding claims, wherein the reaction is carried out in a polar solvent, preferably selected from methanol, ethanol, 2,2,2-trifluoroethanol, n-propanol, isopropanol, water or mixtures thereof.

8. The process of any one of the preceding claims, wherein the reaction is carried out in a temperature range of from -40°C to up to 100°C; preferably, between room temperature and 50°C; most preferably at room temperature.

9. The process of any one of the preceding claims, wherein each of the compounds of formulas (II), (IV) and (V) are initially present in an amount of 0.9-1.3 molar equivalents relative to the amount of the amine of formula (III).

10. The process of any one of the preceding claims, wherein the isocyanide (IV) is prepared in situ from the corresponding formamide of formula (VI):



(VI).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/071880

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 844 775 A1 (ASTELLAS PHARMA INC [JP]) 17 October 2007 (2007-10-17) paragraph [0014] -----	1-10
A	EP 1 652 843 A1 (ASTELLAS PHARMA INC [JP]; RATIONAL DRUG DESIGN LAB [JP]) 3 May 2006 (2006-05-03) paragraph [0031] -----	1-10
A	EP 1 857 108 A1 (ASTELLAS PHARMA INC [JP]) 21 November 2007 (2007-11-21) paragraphs [0019], [0021] -----	1-10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 2019	16/10/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Baston, Eckhard

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/071880

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1844775 A1	17-10-2007	CA 2596850 A1	10-08-2006
		EP 1844775 A1	17-10-2007
		ES 2347681 T3	03-11-2010
		JP WO2006082820 A1	26-06-2008
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		WO 2006082820 A1	10-08-2006
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		BR PI0413430 A	17-10-2006
		CA 2535199 A1	17-02-2005
		CN 1832930 A	13-09-2006
		CY 1115461 T1	04-01-2017
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